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Chronic hypoxia adaptation at high altitude: a perspective on Its potential role in mortality in viral pneumonia-associated ARDS and implications for personalized critical care

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Abstract

Acute respiratory distress syndrome (ARDS) secondary to viral pneumonias, predominantly COVID-19 but also influenza and adenovirus, remains a major ICU mortality driver, with rates exceeding 40%. Chronic high-altitude adaptation (≥ 2,500 m) modifies human pulmonary physiology through hypoxia-inducible factor (HIF-1α/2α) stabilization, ACE2 downregulation, enhanced capillary recruitment, and anti-inflammatory shifts, potentially reducing ARDS severity. Across published observational studies, findings remain heterogeneous; however, several cohorts have reported lower mortality at moderate-to-high altitude (approximately 30–50% in some reports), along with proposed altitude-appropriate SpO_2 targets (89–93%) and alternative interpretations of oxygenation indices (e.g., barometric pressure–adjusted P/F ratios). Protection is strongest in younger, comorbidity-free patients, but attenuates in diabetics/hypertensives. In this perspective, we critically examine the evidence on how altitude may influence the clinical course and survival of critically ill patients, exploring potential pulmonary adaptive mechanisms and reflecting on their implications for monitoring and management in intensive care units.

Keywords High-altitude adaptation, Chronic hypoxia, ARDS, COVID-19, Influenza pneumonia, HIF-1α, Pulmonary physiology, ICU mortality, Personalized critical care, Bedside monitoring

Introduction

Viral pneumonias induced by SARS-CoV-2 (COVID-19), influenza, or adenovirus frequently evolve into acute respiratory distress syndrome (ARDS) [1, 2]. According to the definition, ARDS is characterized by acute onset, bilateral pulmonary infiltrates of non-cardiac origin on chest radiography or computed tomography, and a PaO_2/FiO_2 ratio below 300 mmHg [3]. ICU mortality reaches 40–56%; the potential underlying mechanisms include V/Q mismatch, endothelial injury, cytokine storms (IL-6 > 80 pg/mL), and thrombosis. [4]. Therapeutic goals in ARDS primarily focus on treating the underlying

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cause, such as adequate management of pneumonia, while supportive therapies aim to reduce damage caused by inflammation, fibrosis, and mechanical ventilation itself [5], adjunctive systemic corticosteroids may benefit selected viral pneumonias: they reduce mortality in severe COVID-19, but in influenza have been linked to higher mortality and more nosocomial infections, and in SARS/MERS to delayed viral clearance, supporting etiology-specific use (7,8). In ICU patients with PCR-confirmed respiratory virus–related CAP, corticosteroids were independently associated with lower mortality (adjusted OR 0.46; 95% CI 0.22–0.97), with greater benefit in patients < 70 years [6–8]. In parallel, environmental modifiers like chronic high-altitude exposure (> 2,500 m) emerge as modulators [9, 10].

Hypobaric hypoxia at altitude triggers physiological responses for lowlanders' acclimatization (short-term and reversible adjustments such as tachycardia and hyperventilation, PaO_2 50–67 mmHg) and genetic adaptation in altitude dwellers (EPAS1 variants in Andeans/Tibetans) [11]. Early COVID-19 ecological data showed lower case fatality rates in populations at altitudes above 2,500 m (3.2% vs. 8.6% in lowlands) [12–14]. A synthesis of 40 studies confirms heterogeneity: protection at moderate altitudes but reversal above 4,000 m. Prospective Ecuadorian data (2,850 m vs. sea level) report also showed superior survival at altitude (39 vs. 21 days; HR 0.55) [15]. In this perspective, we critically examine evidence on how altitude may influence the clinical course and survival of critically ill patients, explore potential pulmonary adaptive mechanisms and reflecting on their implications for monitoring and management in intensive care units.

Effect of environmental factors on viruses

Environmental factors may influence viral virulence. In the case of SARS-CoV-2 at high altitude, it has been suggested that dry air and abrupt temperature changes may affect viral virulence [16]; for example, low temperatures may increase the risk of SARS-CoV-2 infection [17]. Ultraviolet (UV) radiation has been shown to damage multiple viral structural components, particularly by inducing damage to viral genomic nucleic acids, including strand breaks, protein–RNA cross-links, and dimers between adjacent pyrimidine residues [18]. In addition, high altitude and low ambient pressure may affect the rate of saliva evaporation and airborne viral transmission. It has been described that saliva droplets evaporate more slowly than water, prolonging their persistence in the air, and that low pressure further extends droplet airborne lifetime, potentially increasing the risk of transmission [19].

Physiological adaptations to high altitude

Acclimatization vs. adaptation

Acclimatization yields reversible physiological adjustments, such as hyperventilation, which raises alveolar PO_2 by 10–15 mmHg, blunting HVR to conserve energy [20, 21]. On the contrary, in biological terms, adaptation implies the existence of heritable traits resulting from natural selection, for instance, Andean/Tibetan EPAS1/EGLN1 variants optimize HIF signaling, reducing polycythemia risks [22].

Ventilatory control adaptations include carotid body hypersensitivity, which increases baseline ventilation by 20–30%. Chronic exposure leads to considerable changes in lung anatomy and function: an expansion of the thorax cavity, with the thoracic volume increasing by 10–15% and respiratory system compliance reaching values of 30.5 mL cmH_2O, compared with 27 mL/cmH_2O initial values [23, 24]. In parallel, vascular remodeling enhances V/Q by reducing the shunt below 10%, while capillary density increases by 20–30% through the VEGF pathway [25, 26],

Among the more conspicuous hematological and cytoprotective adaptations, hypoxia induces an increase in erythropoietin (EPO) that elevates blood hemoglobin content, often reaching 17.4 g/dL, as compared to 14 g/dL in sea level residents. The activation of HIF-1α and HIF-2α pathways upregulates glycolysis, reduces apoptosis, and modulates immune activity by increasing M2 macrophages [27, 28]. a phenotype typically promoted by IL-10 and Th2 cytokines (IL-4/IL-13) and characterized by anti-inflammatory programs (e.g., CD163, HMOX1), which may help limit excessive tissue-damaging inflammation [29, 30].

HIF-1α functions as a heterodimeric transcription factor that plays a central regulatory role in the expression of numerous genes responsive to hypoxia and inflammatory stimuli, and it is essential for regulating immune responses under hypoxic conditions. HIF-2α regulates cellular responses to chronic hypoxia by sustaining genes critical for vascular remodeling and maturation [31, 32]. Additionally, during acute lung injury, HIF-1α activation exhibits cell type–specific effects in the early phases, modulating inflammation, vascular leakage, and remodeling in immune and endothelial cells [32]. However, activation of the mechanistic target of rapamycin (mTOR) signaling pathway facilitates the translocation of HIF-1α from the cytoplasm to the nucleus, leading to increased expression of vascular endothelial growth factor (VEGF), which stimulates angiogenesis while also increasing vascular permeability. This process contributes to pulmonary edema, capillary endothelial damage, and enhanced infiltration of inflammatory mediators [32]. It has been described that HIF-1α production, inflammatory responses, and high mortality occur in elderly patients.

Additionally, the SARS-CoV-2 ORF3a protein induces mitochondrial damage and the production of mitochondrial reactive oxygen species (Mito-ROS), promoting HIF-1α expression, which in turn facilitates SARS-CoV-2 infection and cytokine production [33].

Pulmonary-specific modifications

Within the pulmonary system, high-altitude residents exhibit alterations in gas exchange, inflammation modulation, coagulation balance, and viral entry. Enhanced gas exchange efficiency is due to a 15–20% enlargement of the surface area of alveoli and capillaries, resulting in a normal PaO_2 of 50–67 mmHg at geographical elevations between 3,400 and 4,150 m [34, 35]. Inflammatory adaptation to altitude hypoxia includes IL6 and TNF-α concentrations reduced by 20–30% (Fig. 1), and notable differences in erythropoietin anti-inflammatory effects between survivors and non-survivors of viral pneumonia (7.06 vs. 2.78 mU/mL) [36, 37]. Although platelet counts increase by 15–20% indicating a prothrombotic change, it is countered by NO-mediated vasodilation [12]. Chronic hypoxia downregulates pulmonary ACE2 expression by 30–50%, restraining viral entry, especially with SARS-CoV-2 binding [38, 39]. (Fig. 1)

These adaptations result in altitude-adjusted physiological values, where an arterial oxygen saturation (SpO_2) range of 89–93% is considered optimal. Traditionally, it has been proposed that PaO_2/FiO_2 (P/F) ratios should be mathematically corrected following the Berlin definition by applying a factor based on local barometric pressure (e.g., a correction factor of ~0.71 at 2,850 m). However, recent multicenter evidence suggests that this adjustment equation may be inaccurate for acclimatized patients and often fails to correlate with measured clinical outcomes [40]. Therefore, while this formula remains a theoretical alternative, current practice supported by the 2025 consensus—recommends relying on direct physiological measurements and established reference values for high-altitude residents [41].

Genes

There are different genetic factors that influence performance and tolerance to high altitude. One of the most notable is the polymorphism of the angiotensin-converting enzyme (ACE) gene [42]. It has been reported that mountaineers who have climbed above 7,000 m without the use of supplemental oxygen predominantly carry the homozygous insertion (II) allele of the ACE gene [42]. In a study analyzing unrelated Ladakhi adults who live in Ladakh in India and Tibet in China at altitudes of 3,600 m and above, lowland inhabitants who migrated to Ladakh, and lowland residents, it was observed that the II genotype may be associated with high-altitude adaptation, which could influence physical efficiency [43]. This predominance is not only associated with high-altitude performance; it is also related to the survival of critically ill patients with ARDS [42]. On the other hand, it has been observed that the DD genotype of the ACE gene is a risk factor for poor adaptation to high altitude, and a lower frequency of DD carriers indicates a greater capacity for adapting to high altitude [44].

Mechanisms potentially reducing mortality in viral pneumonia-associated ARDS

Hypoxia tolerance and ARDS pathophysiology

Viral ARDS leads to impaired gas diffusion, reflected by an alveolar-arterial oxygen gradient above 30 mmHg. However, chronic altitude adaptations help counter it by several mechanisms. Oxygen utilization becomes more efficient as HIF-1α enables glycolysis, increasing ATP by 20–30% in hypoxia while simultaneously reducing oxidative stress; additionally, EPO protects endothelium [45, 46]. Gas exchange is optimized by enhanced capillary recruitment which lowers shunt as low as 10–15%, compared to the 20–30% seen at sea-level ARDS [1, 24, 47]. The anti-inflammatory response is also modulated; patients in high altitudes show a shift to M2 macrophages that attenuates the cytokine storms, with IL-6 below 50 pg/mL rather than exceeding 80 pg/mL. The lower neutrophil-to-lymphocyte ratios presented in these patients (frequently below 5.06) have been associated with high chance of survival [10, 48]. However, there are limitations, shown in adenovirus infections above 4,500 m, where cytokines elevate: IL-6 concentration can rise by 50–100% [49].

Evidence from clinical studies

Evidence demonstrates a consistent protective trend associated with moderate altitudes. Survival improved substantially, with a mortally reducing by 30–50%, shown in a hazard ratio of 0.55 and a 74% chance of ICU survival in elevations above 1,500 m (Table 1) [15, 47]. Clinical severity metrics also differed between altitudes; APACHE II scores 9 compared with 8 at 72 h and a higher static compliance (30.5 vs. 27 mL/cmH_2O) [15, 50]. Analysis of subgroups revealed that the strongest effect appeared in younger patients without comorbidities, who survived 49 days, contrasted with 17 days at sea level; this protection is attenuated in metabolic disorders as diabetes, where fatality rates were increased by approximately 97%, showing that altitude-related protection is not uniform across all populations [15].

Additionally, it has been reported that certain population groups residing at high altitudes exhibit polymorphisms of the angiotensin-converting enzyme 2 (ACE2) receptor, which are associated with increased tolerance to hypoxia. Reduced expression or inactivation of ACE2 receptors has been shown to promote a proinflammatory

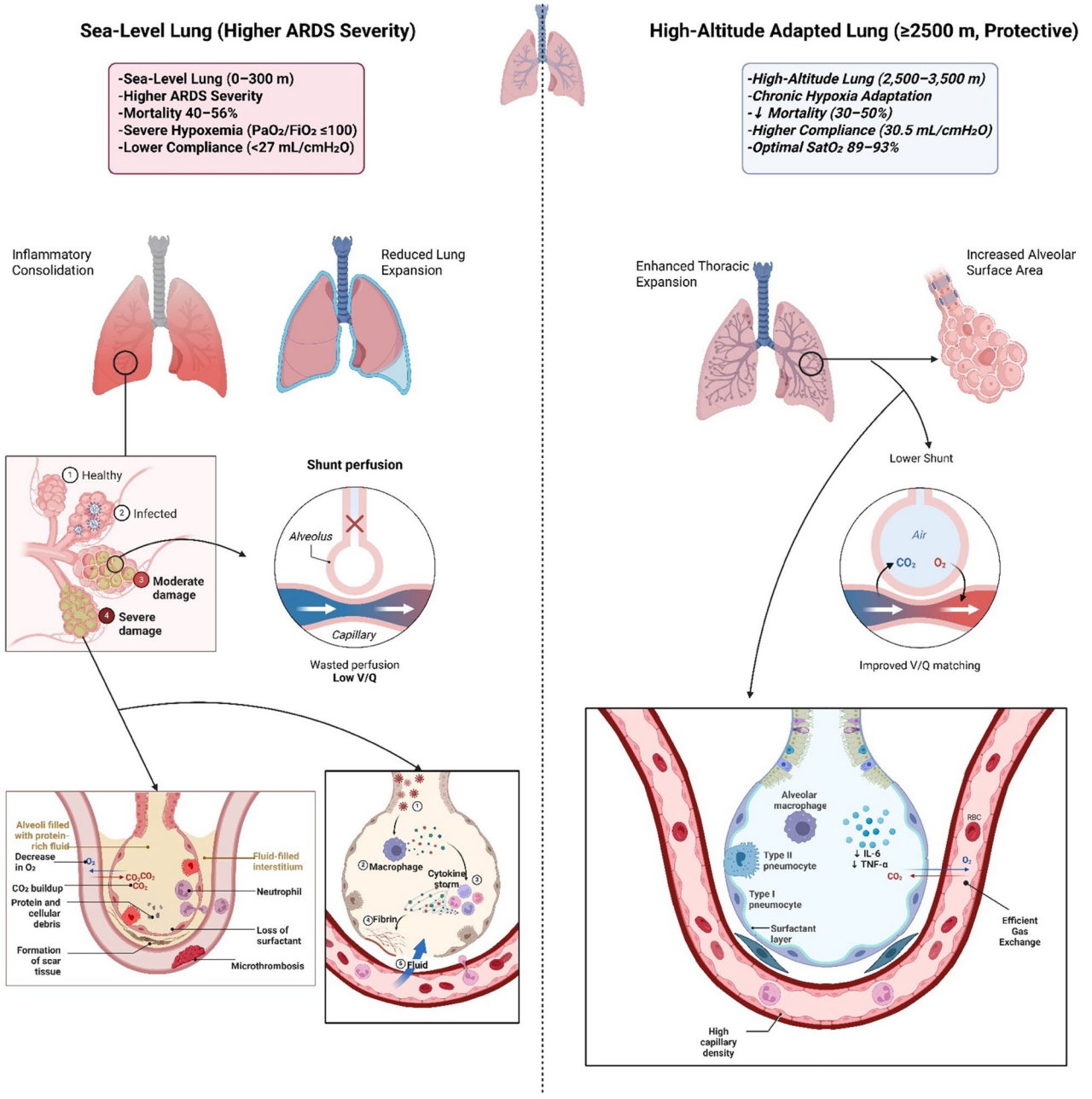

Fig. 1 Comparative Lung Response to Viral Pneumonia: Sea Level Versus High-Altitude Hypoxia Adaptation. This diagram contrasts severe ARDS presentations at sea level (left panel, 0–300 m) with the protective phenotype of chronic high-altitude adaptation (right panel, ≥ 2500 m). Sea-level lungs exhibit higher severity and mortality (40–56%) due to reduced compliance, significant shunt perfusion, and intense inflammation characterized by a cytokine storm, alveolar edema, and microthrombosis. Conversely, high-altitude adapted lungs demonstrate structural adaptations—including increased alveolar surface area and capillary density—that improve ventilation/perfusion matching and compliance. This adaptive phenotype is associated with reduced inflammatory responses (lower IL-6 and TNF-α) and lower mortality rates (30–50%)

state, which may exacerbate pulmonary injury and contribute to multiorgan dysfunction in patients with ARDS [15]. From a clinical perspective, chronic exposure to hypoxemia may induce physiological adaptations that optimize cellular oxygenation, enhance antioxidant defenses, and improve mitochondrial performance at the alveolar level. Furthermore, the elevated erythropoietin levels observed in high-altitude residents may confer a protective effect by stimulating erythropoiesis and heme synthesis, thereby contributing to improved tissue oxygenation [51].

On the other hand, environmental factors should not be overlooked, as they may also have influenced the findings of these studies. It has been described that

Table 1 Clinical and epidemiological studies on the impact of altitude on the severity and mortality of respiratory diseases

Author	Location	Altitude (meters)	Virus type	Study design	Result
Wang et al. 2025 [52]	China	5000	Hypoxia-ALI	Primary (Human/rat/cells)	High-altitude hypoxia triggers lung injury through a reciprocal cycle of epithelial ferroptosis and macrophage inflammation. This study found that Dimethyl fumarate (DMF) mitigates this damage by upregulating the Nrf2/SLC7A11 pathway. These results identify DMF as a potent protective agent against altitude-induced respiratory complications
Vásquez-Gómez et al. 2024 [53]	Bolivia	4,150	COVID – 19	Retrospective	PO_2S is a crucial factor for estimating ICU stays for COVID-19 patients living at high altitudes
Concha-Velasco et al. 2023 [54]	Peru	3,399	COVID – 19	Retrospective cohort, multicenter	Critical illness (vs. moderate) was associated with a higher risk of death (aHR: 1.27; 95% CI: 1.14–1.142), whereas ICU admission (aHR: 0.39; 95% CI: 0.27–0.56), the IRS (aHR: 0.37; 95% CI: 0.26–0.54), a ROX index ≥ 5.3 (aHR: 0.87; 95% CI: 0.80–0.94), and a $SatO_2/FiO_2$ index ≥ 122.6 (aHR: 0.96; 95% CI: 0.93–0.98) were associated with a lower risk of death
Galindo et al. 2021 [55]	Colombia	2,640	COVID-19	Concurrent cohort	Among hospitalized patients with SARS-CoV-2 pneumonia living at high altitude, ICU admission and the use of invasive mechanical ventilation were high. Risk factors such as advanced age, ICU admission, and arterial pH were associated with mortality
Molano-Franco et al. 2024 [56]	Colombia, Bolivia	2,650-4,150	ARDS (not specified)	Cohort study	In high-altitude ICUs, monitoring inflammatory markers may be more beneficial for improving ARDS survival rates than emphasizing respiratory failure markers
Chacon et al. 2020 [57]	Colombia	2,630	ARDS (pediatrics)	Retrospective case series	Pediatric patients with acute respiratory distress syndrome at moderate altitudes exhibit a clinical course similar to those at low altitudes, including mortality rates
Nicolaou et al. 2022 [58]	Peru	0–4,373	COVID-19	Two-stage análisis	Living at high altitude may not confer a lower risk of death from COVID-19
Wang et al. 2021 [59]	Tibet	3,000–4,000	Adenovirus	Retrospective Cohort	Patients with AdVHA infection in high-altitude regions presented severe clinical symptoms and a prolonged disease course
Perez-Padilla et al. 2013 [60]	Mexico	Not specified	Influenza H1N1	Population study	Adjusted hospitalization and in-hospital mortality rates increased with altitude, likely due to the presence of hypoxemia
Molano Franco et al. 2021 [61]	Not specified	> 2,600	Pneumonia	Prospective cohort	High-flow oxygen cannula therapy in patients with hypoxemic respiratory failure living at altitudes above 2,600 m is associated with low rates of therapeutic failure and a reduced need for mechanical ventilation in the ICU
Bautista et al. 2025 [62]	Bolivia	4,150	ARDS	Longitudinal cohort	The ventilatory ratio value stands out as a practical prognostic marker for ARDS at very high altitude; a value greater than 2 on day 5 and age were independently associated with higher mortality

Table 1 (continued)

Author	Location	Altitude (meters)	Virus type	Study design	Result
Ballaz et al. 2021 [63]	Ecuador	2,850	COVID – 19	Retrospective	Changes in the erythrogram parameters were unexpectedly trivial, at least at high altitude, and therefore not consistently associated with COVID-19 pneumonia severity. A reduction of either hemoglobin or red blood cells (RBCs) were not observed in severe COVID-1
Arias-Reyes C, et al. 2020 [12]	Tibet, Ecuador, Boliva	> 2,500	COVID-19	Epidemiological analysis	The physiological acclimatization/adaptation that counterbalance the hypoxic environment in high-altitude may protect from severe impact of acute SARS-CoV-2 virus infection
Cano-Pérez et al. 2020 [14]	Colombia	1–3,180	COVID-19	Epidemiological análisis	The case fatality rate was negatively correlated with the altitude of the cities. The incidence of cases and deaths from COVID-19 had an apparent correlation with altitude; however, these variables were better explained by population density
Campos et al. 2021 [51]	Ecuador	0–3,000	COVID-19	Ecological study	Statistically significant differences were observed in the regions of Amazónica, Sierra, Costa of Ecuador for incidence, mortality, and case fatality rates, suggesting an association between altitude and SARS-CoV-2 transmission and COVID-19 disease severity (p-value ≤ 0.05)
Bridgman et al. 2022 [64]	USA	30 – >3,000	COVID-19	Ecological study	Higher altitude lowering the COVID-19 fatality rate
Jibaja et al. 2022 [65]	Ecuador	> 1,500	COVID-19	Retrospective cohort multicenter study	High altitude is associated with significant higher probabilities of ICU survival/discharge (HR: 1.74 [95% CI: 1.46–2.08]) and hospital survival/discharge (HR: 1.35 [95% CI: 1.18–1.55]) than patients treated at sea level
Chilipio-Chiclla et al. 2023 [66]	Peru	0 – >2,500	COVID-19	Ecological study	An inverse correlation between cumulative incidence rate (1 823 districts) and altitude (Rho: -0.355; $p < 0.001$) was observed, i.e., it decreased at a higher altitude. In turn, there was a direct correlation between case fatality rate (1 526 districts) and altitude (Rho: 0.131; $p < 0.001$), i.e., it increased at a higher altitude
Vélez-Páez et al. 2023 [67]	Ecuador	2,850	COVID-19	Retrospective observational study	Patients with severe COVID-19 and with IL-6 values at 24 h ≥ 11, NLR values at 24 h ≥ 22, and NLR values at 72 h ≥ 14 were 8.3, 3.8, and 3.8 times more likely to die at 28 days, respectively
Vélez-Páez et al. 2023 [68]	Ecuador	2,850	COVID-19	Retrospective cohort study	Selected cut-off values for ferritin (≥ 1225 ng/dl, $p = 0.026$), IL-6 (≥ 11 pg/ml, $p = 0.005$) and NLR (≥ 22, $p = 0.008$) at 24 h, as well as $PaFiO_2$ (≤ 164 mmHg, $p = 0.015$), NLR (≥ 16, $p = p = 0.013$) and SOFA (≥ 6, $p = 0.031$) at 72 h, appear to have good discriminating power to differentiate survivors versus non-survivors

Table 1 (continued)

Author	Location	Altitude (meters)	Virus type	Study design	Result
Tekin et al. [69]	Multinacional	< 500->1000	COVID-19	Observational multinational cohort study	A non-linear association was observed with 28-day mortality following hospital admission (aOR = 0.96 [0.62–1.47], 1.04 [0.92–1.19], 0.49 [0.22–0.90], and 0.51 [0.27–0.98] for altitude levels of 75 m, 125 m, 400 m, and 600 m above sea level, respectively, compared with the reference altitude of 148 m; $p = 0.001$)
Choudhuri et al. [70]	USA	< 1500->2500	Respiratory syncytial virus	Retrospective observational study	The hospitalization rate increased by 25% in infants younger than 1 year and by 53% in children aged 1–4 years for every 1,000-m increase in altitude. The risk of hospitalization was higher at altitudes above 2,500 m
Luo et al. [71]	China	20 and 4,058.40	Pneumonia	Prospective observational study	In the plateau group showed milder clinical manifestations, with shorter duration of fever before admission, lower levels of serum tissue injury markers, and lower incidences of atelectasis
Zhang et al. [72]	Tibet	2500->4500	Pneumonia	Prospective observational study	Multivariate Cox regression analysis showed that the following factors were independently associated with 30-day mortality: age ≥ 65 years (HR = 1.849; 95% CI: 1.012–3.379; $p = 0.046$), septic shock (HR = 4.340; 95% CI: 1.845–10.208; $p = 0.001$), PaO_2/FiO_2 ratio (P/F) < 150 mmHg (HR = 3.333; 95% CI: 1.866–5.952; $p < 0.001$), D-dimer > 3.0 mg/L (HR = 1.965; 95% CI: 1.044–3.699; $p = 0.036$), and unknown etiology (HR = 2.391; 95% CI: 1.319–4.335; $p = 0.004$)
Khan et al. [73]	Pakistan	1675–2590	Pneumonia	Longitudinal cohort study	Among children reported with pneumonia, 28% had multiple episodes. Incidence rates per 100 child-years of observation were 29.9 for pneumonia and 8.1 for severe pneumonia. Factors associated with a high incidence of pneumonia were younger age, male gender and living at high altitude
Simbaña-Rivera et al. 2021 [15]	Ecuador	2,850 vs. 10	COVID – 19	Prospective cohort, two-center	A difference in survival was observed in favor of the high-altitude group ($p = 0.006$), with a median survival of 39 days compared to 21 days in the low-altitude group
Gao et al. 2023 [74]	China	6000	Hypoxia-lung injury	Primary (Rat/cells)	Acute hypoxia triggers lung injury by simultaneously activating distinct pathways for systemic inflammation and coagulation abnormalities. Specifically, pulmonary inflammation is mediated via the HMGB1/RAGE/NF-κB axis, while coagulation dysfunction is driven by the F2/Rho signaling pathway. These molecular insights provide a theoretical basis for developing targeted therapeutic strategies to counteract hypoxia-induced damage

Table 1 (continued)

Author	Location	Altitude (meters)	Virus type	Study design	Result
Tsai et al. 2019 [75]	Taiwan	3100	Hypoxia-vascular leak	Primary (Human/mouse)	Acute hypoxia triggers the expression of miR-424/322, which fine-tunes the HIF-1α-VEGF axis to stabilize the endothelial barrier and prevent leakage. These "hypoximirs" decrease overzealous VEGF expression, directly mitigating the risk of high-altitude pulmonary edema (HAPE)
Hirani et al. 2001 [76]	Ireland	Simulated (PO_2 26mmHg)	Hypoxia-macrophages	Primary (Human/rabbit/cells)	Hypoxia rapidly and selectively upregulates Interleukin-8 (IL-8) in macrophages, which strongly predicts ARDS progression and poor oxygenation (PaO_2/FiO_2 ratio). This induction follows a unique AP-1/C/EBP signaling pathway while simultaneously suppressing other cytokines like TNF-α. These findings define a specific "hypoxic inflammatory signature" critical for early ARDS pathogenesis
Shushanyan et al. 2025 [77]	Armenia	7620	Pulmonary edema	Primary (Rat)	HAPE is driven by the depletion of Nitric Oxide (NO) and antioxidant enzymes (SOD/Catalase), paired with TNF-α and mast cell activation. This biochemical collapse disrupts the alveolar-capillary barrier, leading to edema, fibrosis, and metabolic failure (elevated LDH/Arginase)

high-altitude environments are associated with lower air density and greater intermolecular distances, which could reduce the viral inoculum in the air and decrease the likelihood of person-to-person transmission [12, 51]. In addition, other factors such as population density, access to basic resources, availability of healthcare, and capacity for social distancing may also have contributed to the observed outcomes [51].

Molecular links between hypoxia and ARDS pathophysiology

Hypoxia serves as a pivotal trigger in ARDS pathophysiology at high altitudes, primarily through hypoxia-inducible factor-1α (HIF-1α) stabilization, which orchestrates bidirectional interactions with inflammatory cascades. Under acute hypobaric hypoxia (e.g., simulated 5000–7620 m, FiO_2 10–11%), HIF-1α upregulates downstream genes like VEGFA, BNIP3L, ANGPTL4, and EGLN1, while interfacing with Toll-like receptor 4 (TLR4) signaling to amplify inflammation [52, 78]. This activates convergent pathways: TLR4/NF-κB/NLRP3 promotes cytokine release (e.g., IL-1β fold-increase via NALP3/caspase-1), HMGB1/RAGE/NF-κB drives macrophage-mediated inflammation and coagulation via F2/Rho dysregulation, and EGFR/PI3K/AKT/NF-κB exacerbates oxidative stress [74, 75]. Oxidative mechanisms, such as the ROS-HIF-1α-VEGF axis, directly impair vascular permeability, with causal evidence from siRNA knockdowns showing reduced endothelial leakage in human umbilical vein endothelial cells (HUVECs) and rat models [79] (Fig. 2).

Ferroptosis emerges via Nrf2/SLC7A11 downregulation, leading to epithelial cell death and lipid peroxidation, attenuated by dimethyl fumarate (DMF) activation of Nrf2/GPX4 [52]. Barrier dysfunction arises from Na, K-ATPase endocytosis/degradation, impairing alveolar fluid clearance, coupled with neutrophil hyperactivation through epigenetic H3K4me3 loss, resulting in persistent elastase/MMP9 release and long-term immune dysregulation post-recovery [76, 80]. Temporal dynamics reveal adaptive HIF-1α responses (48 h), explaining heterogeneous outcomes [77].Mechanistic evidence spans correlative (qPCR/Western blot) to causal (inhibitors like TAK-242 for TLR4), with studies in rats and humans highlighting inflammation severity as a mortality correlate over respiratory metrics [81]. These links underscore therapeutic potential in targeting HIF-1α via prolyl hydroxylase domain (PHD) inhibitors or antioxidants, though translational gaps persist in human high-altitude contexts.

Challenges and contradictions

Considerable heterogeneity exists across regions. For example, analysis in Peru (93,528 deaths) found that there is no link between altitude above 1,000 m and mortality, suggesting that elevation does not universally predict improved outcomes [50]. Confounding factors may play an important part in these contradictions. Highlands tend to have younger population with median ages of

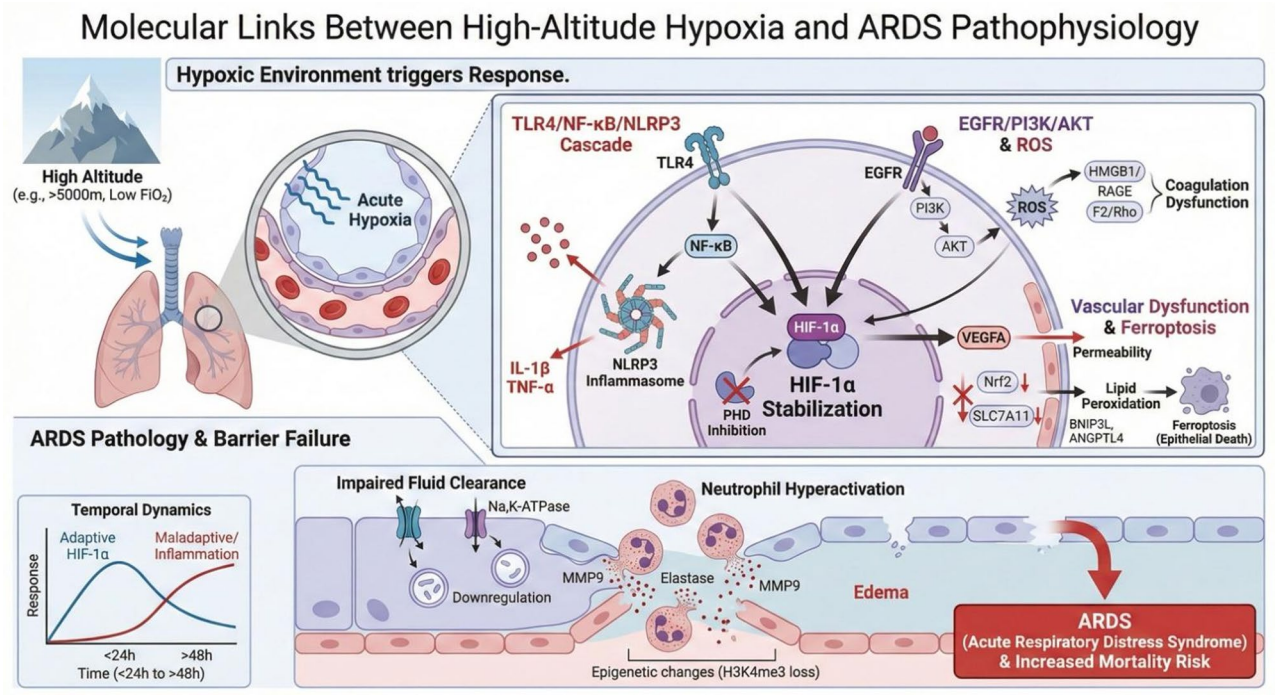

Fig. 2 Acute high-altitude hypoxia (Top Panel) stabilizes HIF-1α by inhibiting PHDs. This triggers divergent signaling (Middle Panel): activation of the TLR4/NF-κB/NLRP3 cascade releases IL-1β and TNF-α; the EGFR/PI3K/AKT axis increases ROS, promoting coagulation via HMGB1/RAGE/F2/Rho; and HIF-1α-driven VEGFA upregulation increases permeability, while Nrf2/SLC7A11 downregulation induces epithelial ferroptosis. Pathophysiological consequences (Bottom Panel) include impaired fluid clearance via Na, K-ATPase internalization and barrier damage by neutrophil-derived elastase and MMP9, causing protein-rich edema. The inset shows HIF-1α responses transition from adaptive (< 24 h) to maladaptive (> 48 h) over time. These mechanisms converge to cause ARDS, with mortality risk linked to inflammation severity

57 years contrasted to 60 years in lower elevations [82]. Disparities in health care access may also strongly influence; as an example mortality rate in Colombia reaches 56% whereas in Ecuador the mortality rate is 35% [82]. Beyond acute outcomes, altitude may also shape post-viral trajectories. In a countrywide Ecuadorian survey ($n = 2{,}103$), high-altitude residents (> 2,500 m) reported a higher prevalence of persistent post-COVID symptoms than low-altitude residents, underscoring that potential protection in acute ARDS does not necessarily translate into reduced long-term morbidity [83].

Implications for ICU management

Bedside physiology integration

In clinical practice, altitude physiology needs to have specific adjustments in monitoring and ventilatory strategies. Electric impedance tomography can be used to evaluate ventilation-perfusion patterns, considering the 20–30% increased alveolar recruitment [84]. Importantly, we refer to EIT as a bedside monitoring tool to support physiological interpretation at altitude; robust evidence of mortality benefit from EIT-guided management in mechanically ventilated patients remains limited. Oxygenation indices must be interpreted using altitude, such as a Respiratory Rate Oxygenation index of at least 4.88 [84]. Ventilatory management targets PEEP levels between 7 and 12 cmH_2O and oxygen saturation goals of 89–93% [68]. Prognosis assessment benefits from close monitoring of the neutrophil-to-lymphocyte ratio, IL-6 levels, and plasma EPO as an additional biomarker of disease severity and survival [85]. On the other hand, the Expert Committee on Critical Medicine at Altitude of the Pan American and Iberian Federation of Critical Medicine and Intensive Care recommends initiating oxygen therapy at high altitudes in medium altitudes (1,500 to 2,500 masl) when arterial oxygen saturation (SaO_2) is < 90%, in high altitudes (2,500 to 3,500 masl) when SaO_2 is < 88%, and in very high altitudes (3,500 to 4,380 masl) when SaO_2 is < 86% [86]. It also establishes that the oxygenation goals at altitude are: in medium altitudes (1,500 to 2,500 masl) SaO_2 92% and PaO_2 75 mmHg; in high altitudes (2,500 to 3,500 masl) SaO_2 90% and PaO_2 70 mmHg; and in very high altitudes (3,500 to 4,380 masl) SaO_2 88% and PaO_2 60 mmHg.4.2 [86].

Future directions

It is necessary for future research to conclusively demonstrate that high altitude is truly protective against ARDS. To this end, controlled clinical trials should evaluate erythropoietin using anti-inflammatory dosing strategies to assess potential protective effects. Genetic studies focusing on EPAS1 could further clarify how heritable

high-altitude adaptations influence ARDS severity and clinical outcomes. In addition, prospective cohort studies comparing respiratory infections (e.g., influenza) at high versus low altitude are required to establish whether any observed protective patterns extend to other pulmonary pathogens. Mechanistic investigations are also essential to define more precisely the molecular links between hypoxia and ARDS pathophysiology. From a clinical epidemiology standpoint, future work should prioritize prospective, multicenter high- versus low-altitude comparisons with harmonized ICU protocols and predefined oxygenation targets, combined with rigorous control of confounding (e.g., age, comorbidities, severity scores, population density, access to care, and referral patterns) using methods such as propensity weighting or matched cohort designs.

Conclusions

In moderate-to-high altitude settings (≈2,500–3,500 m), some observational studies have reported lower mortality among patients with viral pneumonia–associated ARDS, although results are heterogeneous and likely influenced by confounding (e.g., population structure, access to care, and case mix). Proposed explanatory pathways include HIF-mediated responses, ACE2 modulation, improved lung microcirculation, and a more favorable inflammatory profile. In this setting, lower SpO_2 targets (89–93%) and altitude-adjusted PaO_2/FiO_2 and NLR thresholds reflect an adapted physiological baseline rather than treatment failure. ICU management at altitude should therefore move away from sea-level cut-offs and adopt altitude-specific thresholds, and monitoring strategies, acknowledging that the protective effect is strongest in younger, non-comorbid patients and becomes heterogeneous at very high altitudes or among patients burdened by significant comorbidity.

Abbreviations

ACE	Angiotensin-converting enzyme
ACE2	Angiotensin-converting enzyme 2
AdVHA	Adenovirus infection at high altitude (as reported in the cited study)
aHR	Adjusted hazard ratio
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
CAP	Community-acquired pneumonia
CD163	Cluster of differentiation 163
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DD	Deletion/deletion genotype (ACE gene)
ECMO	Extracorporeal membrane oxygenation
EGLN1	Egl nine homolog 1
EPO	Erythropoietin
EPAS1	Endothelial PAS domain protein 1
FiO_2	Fraction of inspired oxygen
HIF	Hypoxia-inducible factor
HIF-1α	Hypoxia-inducible factor 1 alpha
HIF-2α	Hypoxia-inducible factor 2 alpha
HMOX1	Heme oxygenase 1
HPAS	Hospital Pablo Arturo Suárez
HR	Hazard ratio
HVR	Hypoxic ventilatory response
ICU	Intensive care unit
IL-10	Interleukin 10
IL-13	Interleukin 13
IL-4	Interleukin 4
IL-6	Interleukin 6
II	Insertion/insertion genotype (ACE gene)
IRS	(as used in the cited study; not defined in the provided text)
masl	Meters above sea level
M2	Alternatively activated macrophages (M2 phenotype)
MERS	Middle East respiratory syndrome
NLR	Neutrophil-to-lymphocyte ratio
NO	Nitric oxide
OR	Odds ratio
$PaFiO_2$	PaO_2/FiO_2 ratio
PaO_2	Arterial partial pressure of oxygen
PCR	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
P/F	PaO2/FiO2 ratio
PO_2	Partial pressure of oxygen
ROX	ROX index (SpO_2/FiO_2 to respiratory rate index)
SaO_2	Arterial oxygen saturation
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SatO2	Oxygen saturation
S/F	SpO_2/FiO_2 ratio
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral oxygen saturation
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
V̇/Q	Ventilation/perfusion ratio

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Generative AI declaration.

The authors employed AI technologies to refine the manuscript's readability and identify typographical errors. AI tools were also used for the aesthetic and technical improvement of Fig. 2. The authors maintain full accountability for the accuracy and integrity of the final work.

Author contributions

Conceptualization: EOP; methodology: EOP, JIC, JVG; resources: MPCP, JLV, JVG, JSIC, and MV; software: EOP, JIC; validation: JLV, GV, EOP; formal analysis: MPCP, JLV, JVG, JSIC, and MV; writing—original draft preparation: EOP, MPCP, JLV, JVG, JSIC, and MV; writing—review and editing: all authors; visualization: JLV, GV, EOP; supervision: EOP; project administration: EOP. All authors have read and approved the final version of the manuscript. JSIC is the corresponding author.

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Data availability

No datasets were generated or analysed during the current study. All data discussed are available in the published sources cited in the manuscript. Additional information is available from the corresponding author upon reasonable request.

Declarations

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Competing interests

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